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COMMENT

A Possible Role for Reproductive Hormones in Newborn Boys: Progressive Hypogonadism without the Postnatal Testosterone Peak

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ABSTRACT

Healthy boys have a considerable production of reproductive hormones during the first postnatal months, the biological significance of which is poorly understood. We report on cases of male infants with hypogonadism (hypogonadotropic hypogonadism, n = 1; panhypopituitarism, n = 2) who showed lack of penile growth and involution of the scrotum. In two boys, diagnoses were obtained in early infancy and hormonal measurements at 3–4 months of age showed serum testosterone levels below detection limits in both low inhibin B (37 and 199 pg/mL, respectively; normal range, 193–563 pg/mL) and low to undetectable gonadotropins [LH, undetectable and 0.07 IU/L (normal range, 0.65–2.69 IU/L), respectively; FSH, 0.18 IU/L in both (range, 0.86–2.52 IU/L)]. In a third boy, gonadotropin deficiency was diagnosed at 3 yr of age by undetectable serum levels of FSH and LH both before and after stimulation with GnRH. All cases required hormonal treatment with testosterone, administered as suppositories in daily doses between 1 and 5 mg, which reintroduced male genital development. Our observations suggest that normal phallic and scrotal development in humans is dependent on intact testosterone secretion during early infancy. Additionally, the diagnosis of gonadotropin deficiency may be established in a short-time window postnatally by measurement of spontaneous serum concentrations of reproductive hormones. (*J Clin Endocrinol Metab* **85:** 4905–4907, 2000)

IT HAS BEEN known for many years that there is a considerable pituitary and testicular hormone production with respect to gonadotropins, testosterone, dihydrotestosterone, and inhibin B in the first postnatal months of life (1–8). However, the physiological and pathological significance of this peak in humans has, until now, been poorly understood.

We report on three cases of infants with male hypogonadism of different etiology who showed progressive involution of their external genitalia during early infancy despite replacement of other pituitary deficiencies. Our observations suggest that the postnatal peak in reproductive hormones plays an important role in genital development.

Materials and Methods

Serum LH and FSH were measured by time-resolved immunofluorometric assays (Delfia; Wallac, Inc., Turku, Finland) with detection limits of 0.06 and 0.05 U/L, respectively. Intra- and interassay coefficients of variation were less than 8% in both assays. Serum testosterone was measured by RIA (Coat-a-Count; Diagnostic Products, Los Angeles, CA) with a detection limit of 0.23 nmol/L and intra- and interassay coefficients of variation less than 10%. Serum inhibin B was measured by specific enzyme-linked immunosorbent assay (9) with a detection limit of 18 pg/mL, and the intra- and interassay coefficients of variations were 15% and 18%, respectively. Patient serum hormone measurements at 3–4 months of age were compared with age-specific longitudinal normal values in healthy boys (4). The normal 95% ranges were: serum testosterone, 0.43–7.71 nmol/L; inhibin B, 193–563 pg/mL; FSH, 0.86–2.52 IU/L; LH, 0.65–2.69 IU/L. Testosterone treatment was administered as suppositories of 1 or 5 mg, manufactured by the hospital's pharmacy using a modification of the method of Hamburger (10). It is well documented that androgen replacement therapy using testosterone suppositories is effective (11).

Case reports

Case 1 (hypogonadotropic hypogonadism). This was the fourth child of consanguinous Turkish parents. There was a maternal history of hyposmia. The genitalia was described as normal male at birth with descended testicles and by a pediatrician at 1 month of age. The patient was referred at 4 months of age because of progressive atrophy of the external genitalia. The penis consisted of a small skinfold with practically no palpable corpora (Fig. 1a). Both testes were inguinal, and the scrotum was hypoplastic. The diagnosis of hypogonadotropic hypogonadism was established as: spontaneous serum LH and testosterone were unmeasurable, and both FSH and inhibin B were low with 0.18 IU/L and 37 pg/mL, respectively. Human CG stimulation with 100 IU/kg twice weekly for 3 weeks increased serum testosterone to 8.01 nmol/L. Treatment with testosterone suppositories was started at 6 months of age (1 mg twice daily for 5 months, hereafter 5 mg daily for 5 months), showing reasonable response (Fig. 1b).

Case 2 (panhypopituitarism). The patient was referred at the age of 1½ yr after a long period of severe failure to thrive and of attacks of hypoglycemia. There was a diagnosis of GH deficiency in one maternal uncle. GH deficiency was diagnosed initially, followed by successive development of other pituitary insufficiencies. Despite adequate substitution therapy (daily doses: recombinant human GH, 2 IU/m^2 sc; hydrocortisone, 12 mg/m^2; T_4, 75 μg; desmopressin, 2.25 mg), the patient developed micropenis as well as a hypoplastic scrotum, and both testes ascended to high scrotal position. LH and FSH were unmeasurable both before and after stimulation with 100 μg GnRH iv at the age of 3 yr. Repetitive measurements of spontaneous serum testosterone levels from

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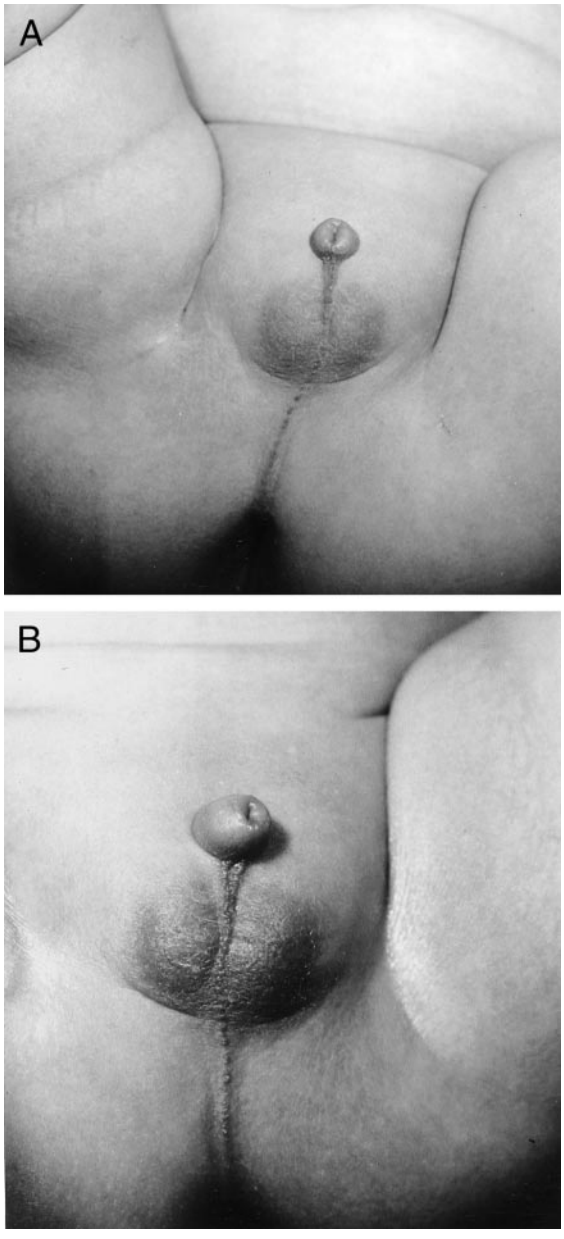

FIG. 1. Patient with hypogonadotropic hypogonadism before (a) and 8 months after (b) treatment with testosterone suppositories.

the age of 2 yr were undetectable. Testosterone increased to 3.16 nmol/L after stimulation with two weekly sc injections of 100 IU human CG/kg for 3 weeks. Thus, the patient showed signs of gonadotropin insufficency. At the age of 4 yr, treatment with testosterone suppositories was initiated with 5 mg daily for 2 months and every second day for 4 months thereafter. There was a significant effect on genital growth.

Case 3 (panhypopituitarism). Case 3 was the brother to case 2. He was diagnosed with adrenal insufficiency at birth. Clinical appearance of the external genitalia was normal at birth with both testes in the scrotum measuring 1 mL each. Overt hypothyroidism and GH deficiency developed at 2 and 7 months, respectively, and the patient was substituted (daily doses: hydrocortisone, 12 mg/m^2; T_4, 50 μg; recombinant human GH, 2 IU/m^2 sc). From the age of 3½ months, the external genitalia became progressively embedded in prepubic fat, and the testes ascended to a nonpalpable position (Fig. 2a). Measurement of spontaneous hormonal values showed undetectable serum testosterone, low FSH, LH, and inhibin B with 0.18 IU/L, 0.07 IU/L, and 199 pg/mL, respectively.

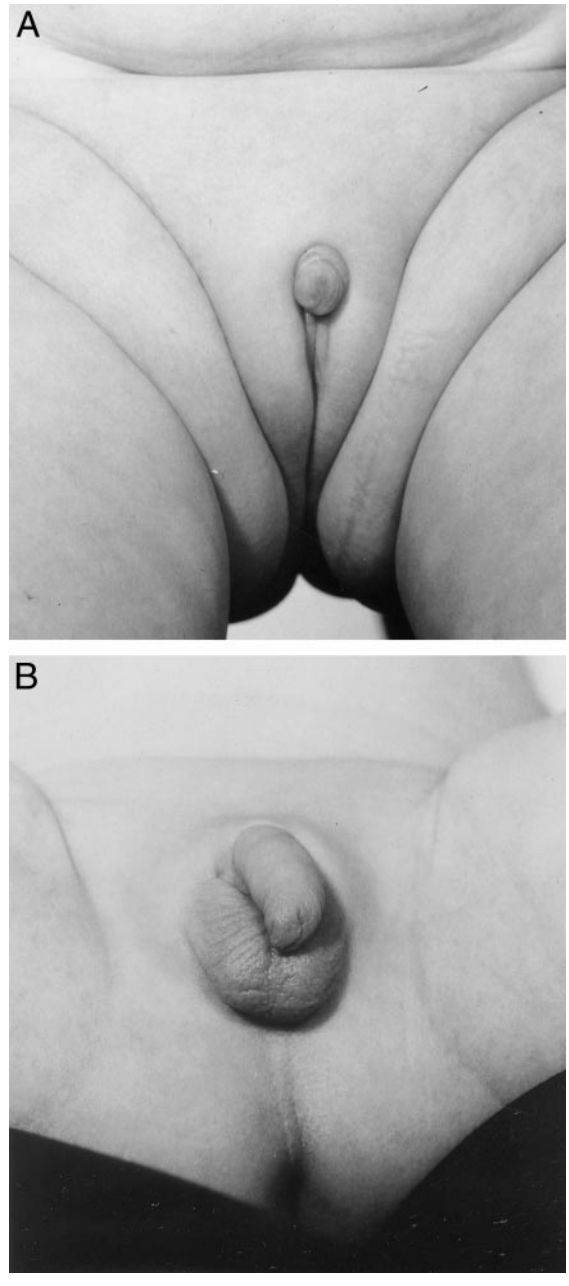

FIG. 2. Patient with panhypopituitarism before (a) and 3 months after (b) treatment with testosterone suppositories.

Because of development of a hypoplastic scrotum and lack of penile growth treatment with testosterone suppositories, 1 mg daily was initiated at 9 months, followed by 1 mg twice daily from 11–14 months of age. There was a significant effect on genital development with penile and scrotal growth and regression of the prepubic fat layer (Fig. 2b).

All patients showed normal psychomotoric development, normal birth weight (3410–4000 g) and length (50–53 cm), and normal male karyotype (46,XY).

Oral permission for publication of the figures was obtained from the parents.

Discussion

Our observations strongly suggest a significant physiological role of the postnatal peak in testosterone for genital development in newborn boys. All three patients had normal

genitalia at birth but showed progressively impaired development (*i.e.* lack of penile growth and involution of the scrotum). In two boys it could be demonstrated that they were lacking the early physiological rise in testosterone. To our knowledge, this is the first report to document that a diagnosis of gonadotropin deficiency may be established in a short-time window postnatally, when the physiological surge of reproductive hormones should occur. The third patient was diagnosed to have gonadotropin deficiency at the age of 3 yr and was, therefore, most likely also lacking the early postnatal surge in reproductive hormones. Normal male genital development could be reestablished with administration of exogenous testosterone.

Although it has been known for a considerable number of years that reproductive hormones increase during early infancy, their biological significance has not been extensively investigated (1–8). It has been a matter of debate as to whether androgens are biologically active during early infancy or not. Microphallus, as one of the symptoms of hypogonadotropic hypogonadism, has, thus, mainly been attributed to the lack of intrauterine stimulation of the fetal testes by gonadotropins during the second trimester (12). Serum concentrations of sex hormone-binding globulins increase during the same period as gonadotropins and testosterone, which may indicate that there is little free, biologically active testosterone available. According to this hypothesis, it has been shown by one group that morning salivary testosterone, representing the free fraction of testosterone, does not increase around 3 months of age in humans (13). Other investigators, however, have found an increase of free testosterone in serum (8). Our cases demonstrate for the first time that the symptoms of micropenis and maldescended testis also are associated with the lack of the early postnatal peak in reproductive hormones.

Our observations are in accordance with data from investigations of primates. A recent study of rhesus macaques indicated that at least part of the circulating testosterone is biologically active (14), because penile and clitoris growth could be significantly altered by suppressing or augmenting testosterone levels. Other intervention studies in primates, suppressing the postnatal androgen increase, have similarly been able to reproduce clinical pictures of hypogonadism (14–16), both with respect to physical maturation and to sexual behavior. The effects could, in some investigations, be followed into adult life with late onset of puberty, attenuated pubertal growth spurt, diminished testicular growth, and reduced sperm count (17–19). Recently, it was demonstrated that neonatal GnRH antagonist treatment compromised Sertoli cell replication in the marmoset (20).

There is also some evidence for a role of gonadotropins and androgens in human infant testicular development with respect to Leydig cell proliferation and germ cell differentiation (21). The penile growth rate during the early postnatal period is small, with an average of 0.17 cm/yr (12). However, this growth rate seems important to parallel the considerable increase in total body length during the same period. In all our patients, the external genitalia responded to androgen treatment with significant growth of the penis and scrotum.

In conclusion, our observations support the hypothesis that the postnatal surge in pituitary and testicular hormone secretion in human infants has a significant biological role in the normal development of the male genitalia. Thus, symptoms of hypogonadism are not only related to the lack of hormone production *in utero* or during puberty. Our observations may be clinically applicable for diagnosing gonadotropin and/or androgen deficiency in patients with genital maldevelopment by early postnatal measurement of spontaneous serum concentrations of reproductive hormones. It remains to be seen whether or not the early effects on genital growth and development are also of significance for adult reproductive function.

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